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Signed P. Mahoney

Dated 2 February 2000

The Patent Office

GB9902047.1.

By virtue of a direction given under Section 30 of the Patents Act 1977, the application is proceeding in the name of

CEREBRUS PHARMACEUTICALS LIMITED,
Incorporated in the United Kingdom,
Oakdene Court,
613 Reading Road,
Winnersh,
WOKINGHAM,
RG41 5UA,
United Kingdom

[ADP No. 07745409001]

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Cardiff Road
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1. Your reference

P020831GB/PNH

2. Patent application number
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3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

CEREBRUS LIMITED
OAKDENE COURT
613 READING ROAD
WINNERSH
WORKINGHAM
RG41 5UA

SECTION 30(1) - ACT APPLICATION FILED 27-5-99

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

UNITED KINGDOM

GB 9851058

4. Title of the invention

CHEMICAL COMPOUNDS XI

5. Name of your agent *(if you have one)*

Carpmaels & Ransford

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

43 Bloomsbury Square
London
WC1A 2RA

Patents ADP number *(if you know it)*

83001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Number of earlier application	Date of filing *(day / month / year)*

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b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body

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11. I/We request the grant of a patent on the basis of this application.

Signature: Carpmaels & Ransford — Date: 29th January 1999

12. Name and daytime telephone number of person to contact in the United Kingdom

PAUL N. HOWARD **0171 242 8692**

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CHEMICAL COMPOUNDS XI

The present invention relates to pyrazinoindole derivatives, to pharmaceutical compositions containing them and to their medicinal use. The active compounds of the present invention are useful in treating obesity and other disorders.

It has been recognised that obesity is a disease process influenced by environmental factors in which the traditional weight loss methods of dieting and exercise need to be supplemented by therapeutic products (S. Parker, "Obesity: Trends and Treatments", *Scrip Reports*, PJB Publications Ltd, 1996).

Whether someone is classified as overweight or obese is generally determined on the basis of their body mass index (BMI) which is calculated by dividing body weight (kg) by height squared (m^2). Thus, the units of BMI are kg/m^2 and it is possible to calculate the BMI range associated with minimum mortality in each decade of life. Overweight is defined as a BMI in the range 25-30kg/m^2, and obesity as a BMI greater than 30 kg/m^2. There are problems with this definition in that it does not take into account the proportion of body mass that is muscle in relation to fat (adipose tissue). To account for this, obesity can also be defined on the basis of body fat content: greater than 25% and 30% in males and females, respectively.

As the BMI increases there is an increased risk of death from a variety of causes that is independent of other risk factors. The most common diseases with obesity are cardiovascular disease (particularly hypertension), diabetes (obesity aggravates the development of diabetes), gall bladder disease (particularly cancer) and diseases of reproduction. Research has shown that even a modest reduction in body weight can correspond to a significant reduction in the risk of developing coronary heart disease.

Compounds marketed as anti-obesity agents include Orlistat (Reductil ®) and Sibutramine. Orlistat (a lipase inhibitor) inhibits fat absorption directly and tends to produce a high incidence of unpleasant (though relatively harmless) side-effects such as diarrhoea. Sibutramine (a mixed 5-HT/noradrenaline reuptake inhibitor) can increase blood pressure and heart rate in some patients. The serotonin releaser/reuptake

inhibitors fenfluramine (Pondimin®) and dexfenfluramine (Redux™) have bee reported to decrease food intake and body weight over a prolonged period (greater than 6 months). However, both products were withdrawn after reports of preliminary evidence of heart valve abnormalities associated with their use. There is therefore a need for the development of a safer anti-obesity agent.

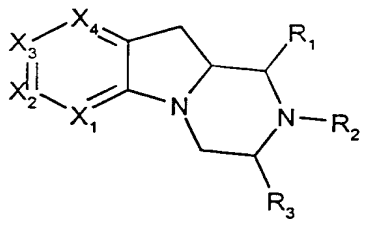
The non-selective 5-HT_{2C} receptor agonists/partial agonists m-chlorophenylpiperazine (mCPP) and trifluoromethylphenylpiperazine (TFMPP) have been shown to reduce food intake in rats (G.A. Kennett and G. Curzon, *Psychopharmacol.,* 1988, 98, 93-100; G.A. Kennett, C.T. Dourish and G. Curzon, *Eur. J. Pharmacol.,* 1987, 141, 429-453) and to accelerate the appearance of the behavioural satiety sequence (S.J. Kitchener and C.T. Dourish, *Psychopharmacol.,* 1994, 113, 369-377). Recent findings from studies with mCPP in normal human volunteers and obese subjects have also shown decreases in food intake. Thus, a single injection of mCPP decreased food intake in female volunteers (A.E.S. Walsh *et al.*, *Psychopharmacol.,* 1994, 116, 120-122) and decreased the appetite and body weight of obese male and female subjects during subchronic treatment for a 14 day period (P.A. Sargeant *et al.*, *Psychopharmacol.,* 1997, 113, 309-312). The anorectic action of mCPP is absent in 5-HT_{2C} receptor knockout mutant mice (L.H. Tecott *et al.*, *Nature,* 1995, 374, 542-546) and is antagonised by the 5-HT_{2C} receptor antagonist SB-242084 in rats (G.A. Kennett *et al.*, *Neuropharmacol.,* 1997, 36, 609-620). It seems therefore that mCPP decreases food intake via an agonist action at the 5-HT_{2C} receptor. However, although both mCPP and TFMPP exhibit high affinity for the 5-HT_{2C} receptor they are both non-selective, having appreciable activity at other 5-HT receptors (G.A. Kennett, *Curr. Opin. Invest. Drugs,* 1993, 2, 317-362).

The preparation of pyrazino[1,2-a]indoles as serotonergic agents, useful as antidepressants and anxiolytics, is disclosed in PCT application WO 9612721. The compounds of this invention are reported to possess high affinity for the serotonergic 5-HT_{1A} receptor. Substituted pyrazino[1,2-a]indoles are used as intermediates in the preparation of heterocyclyl O-substituted alcoholamines as fibrinogen receptor antagonist products as disclosed in PCT application WO 9800401. Pyrazino[1,2-a]indole derivatives are also reported in the preparation of 3-piperazinomethylpyrrolo[2,3-b]pyridines as dopamine D4 receptor antagonists as

disclosed in US 5576319 and WO 9420497. 1,2,3,4,4a,5-Hexahydropyrazino[1,2-a]indole and 3-ethyl-1,2,3,4,4a,5-hexahydropyrazino[1,2-a]indole are disclosed in *Med. Chem. Res.*, 1993, 3, 240-248 and their 5-HT_{1A} and 5-HT_2 binding affinity reported. The 5-HT_{1A} and 5-HT_2 binding affinity for 1,2,3,4,4a,5-hexahydropyrazino[1,2-a]indole is reported to be the same as that observed for 1-phenylpiperazine and demonstrates an approximate ten fold selectivity for 5-HT_{1A} receptors.

It is an object of this invention to provide selective, directly acting 5-HT_2 receptor ligands for use in therapy and particularly for use as anti-obesity agents. It is a further object of this invention to provide directly acting ligands selective for 5-HT_{2B} and/or 5-HT_{2C} receptors, for use in therapy and particularly for use as anti-obesity agents. It is a further object of this invention to provide selective, directly acting 5-HT_{2C} receptor ligands, preferably 5-HT_{2C} receptor agonists, for use in therapy and particularly for use as anti-obesity agents.

According to the present invention there is provided a chemical compound of formula (I):



(I)

wherein:

R_1 to R_3 are independently selected from hydrogen and lower alkyl;

X_1 is selected from N and C-R_4;

X_2 is selected from N and C-R_5;

X_3 is selected from N and C-R_6;

X_4 is selected from N and C-R_7;

R_4, R_5 and R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, alkoxy, aryloxy, alkoyl, aryloyl, alkylthio, arylthio, alkylsulfoxyl, arylsulfoxyl,

alkylsulfonyl, alkoyl, aryloyl, arylsulfonyl, amino, alkylamino, dialkylamino, nitro, cyan carboalkoxy, carboaryloxy and carboxy;

R_6 is selected from hydrogen, halogen, alkyl, aryl, aryloxy, alkylthio, arylthio, alkylsulfoxyl, arylsulfoxyl, alkylsulfonyl, arylsulfonyl, amino, alkylamino, dialkylamino and cyano; with the proviso that R_4 to R_7 are not all selected as hydrogen.

Compounds of the present invention include salts and addition compounds of the compounds of formula (I). The present invention also includes prodrugs which are metabolised in vivo to a compound of formula (I).

As used herein, the term "lower alkyl" means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic, the lower alkyl group is preferable C_5, C_6 and C_7. Where acyclic, the lower alkyl group is preferably methyl, ethyl, propyl or butyl, more preferably methyl.

As used herein, the term "alkyl" means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic, the alkyl group is preferably C_3 to C_{12}, more preferably C_5 to C_{10}, more preferably C_5, C_6 or C_7. Where acyclic, the alkyl group is preferably C_1 to C_{10}, more preferably C_1 to C_6, more preferably methyl, ethyl, propyl or butyl, more preferably methyl.

As used herein, the term "aryl" means an aromatic group, such as phenyl or naphthyl, or a heteroaromatic group containing one or more, preferably one, heteroatom, such as pyridyl, pyrrolyl, furanyl and thiophenyl.

The alkyl and aryl groups may be substituted or unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 substituent. Substituents may include:

carbon containing groups such as

- alkyl,
- aryl, arylalkyl (e.g. substituted and unsubstituted phenyl, substituted and unsubstituted benzyl);

halogen atoms and halogen containing groups such as

haloalkyl (e.g. trifluoromethyl);

oxygen containing groups such as

alcohols (e.g. hydroxy, hydroxyalkyl, aryl(hydroxy)alkyl),

ethers (e.g. alkoxy, alkoxyalkyl, aryloxy, aryloxyalkyl),

aldehydes (e.g. carboxaldehyde),

ketones (e.g. alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylalkylcarbonyl, arylcarbonylalkyl)

acids (e.g. carboxy, carboxyalkyl),

acid derivatives such as esters (e.g. alkoxycarbonyl, alkoxycarbonylalkyl, alkycarbonylyoxy, alkycarbonylyoxyalkyl)

and amides (e.g. aminocarbonyl, mono- or dialkylaminocarbonyl, aminocarbonylalkyl, mono- or dialkylaminocarbonylalkyl, arylaminocarbonyl);

and carbamates (eg. alkoxycarbonylamino, aryloxycarbonylamino, aminocarbonyloxy, mono- or dialkylaminocarbonyloxy, arylaminocarbonyloxy),

and ureas (eg. mono- or dialkylaminocarbonylamino or arylaminocarbonylamino);

nitrogen containing groups such as

amines (e.g. amino, mono- or dialkylamino, aminoalkyl, mono- or dialkylaminoalkyl),

azides,

nitriles (e.g. cyano, cyanoalkyl),

nitro;

sulfur containing groups such as

thiols, thioethers, sulfoxides, and sulfones

(e.g. alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, arylthio, arylsulfinyl, arylsulfonyl, arylthioalkyl, arylsulfinylalkyl, arylsulfonylalkyl);

and heterocyclic groups containing one or more, preferably one, heteroatom, (e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, oxadiazolyl, thiadiazolyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, piperazinyl, morpholinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl and carbolinyl).

As used herein, the term "alkoxy" means alkyl-O- and "alkoyl" means alkyl-CO.

As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical, preferably a fluorine or chlorine radical.

Preferably, R_1 is hydrogen or methyl, more preferably hydrogen.

Preferably, R_2 is hydrogen or methyl, more preferably hydrogen.

Preferably, R_3 is hydrogen or methyl, more preferably hydrogen.

Preferably, R_1, R_2 and R_3 are each independently selected from hydrogen and methyl. More preferably, R_1 and R_3 are independently selected from hydrogen and methyl, and R_2 is hydrogen. More preferably, R_1, R_2 and R_3 are hydrogen.

Preferably, X_1 is C-R_4.

Preferably, X_2 is C-R_5.

Preferably, X_3 is C-R_6.

Preferably, X_4 is C-R_7.

Preferably X_2 is C-R_5 , X_3 is C-R_6 and X_4 is C-R_7.

R_4, R_5 and R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl (including cycloalkyl, halo-alkyl (such as trifluoromethyl) and arylalkyl), aryl, alkoxy (including arylalkoxy), aryloxy, alkoyl, aryloyl, alkylthio, arylthio, alkylsulfoxyl, arylsulfoxyl, alkylsulfonyl, arylsulfonyl, amino, alkylamino, dialkylamino, nitro, cyano, carboalkoxy, carboaryloxy and carboxy.

R_6 is selected from hydrogen, halogen, alkyl (including cycloalkyl, halo-alkyl (such as trifluoromethyl) and arylalkyl), aryl, aryloxy, alkylthio, arylthio, alkylsulfoxyl, arylsulfoxyl, alkylsulfonyl, arylsulfonyl, amino, alkylamino, dialkylamino and cyano.

Preferably, two of R_4, R_5, R_6 and R_7 are hydrogen.

Preferably R_5 and R_6 are independently selected from hydrogen, chlorine, fluorine, trifluoromethyl and bromine. More preferably, at least one of the R_5 and R_6 is selected from chlorine, fluorine, trifluormethyl and bromine.

The compounds of the invention may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. The

compounds can be, for example, racemates or optically active forms. The optically active forms can be obtained by resolution of the racemates or by asymmetric synthesis.

According to a further aspect of the invention, there is provided a compound of formula (I) for use in therapy.

The compounds of formula (I) may be used in the treatment (including prophylactic treatment) of disorders associated with 5-HT_2 receptor function. The compounds may act as receptor agonists or antagonists. Preferably, the compounds may be used in the treatment (including prophylactic treatment) of disorders associated with 5-HT_{2B} and/or 5-HT_{2C} receptor function. Preferably, the compounds may be used in the treatment (including prophylactic treatment) of disorders where a 5-HT_{2C} receptor agonist is required.

The compounds of formula (I) may be used in the treatment or prevention of central nervous disorders such as depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioural disorders, behavioural disorders associated with dementia, organic mental disorders, mental disorders in childhood, aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol addiction, obesity, bulimia, anorexia nervosa or premenstrual tension; damage of the central nervous system such as by trauma, stroke, neurodegenerative diseases or toxic or infective CNS diseases such as encephalitis or meningitis; cardiovascular disorders such as thrombosis; gastrointestinal disorders such as dysfunction of gastrointestinal motility; diabetes insipidus; and sleep apnea.

According to a further aspect of the invention, there is provided use of a compound of formula (I) in the manufacture of a medicament for the treatment (including prophylaxis) of the above-mentioned disorders. In a preferred embodiment, there is provided use of a compound of formula (I) in the manufacture of a medicament for the treatment (including prophylaxis) of obesity.

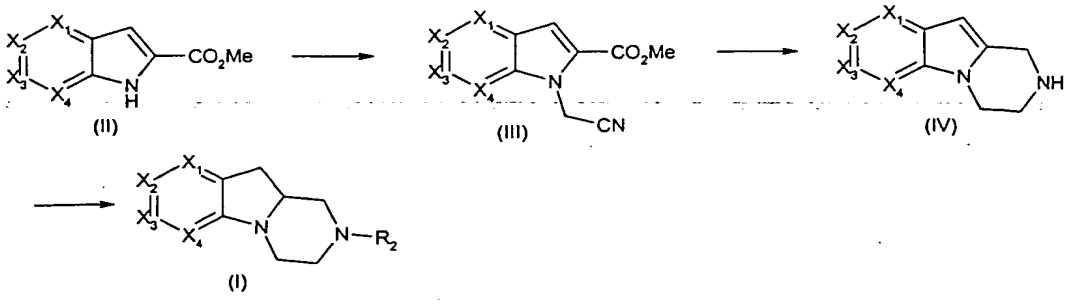
According to a further aspect of the invention, there is provided a method of treating a disorder selected from the group consisting of the above-mentioned disorders comprising administering to a patient in need of such treatment an effective dose of a compound of formula (I). In a preferred embodiment, there is provided a method of treatment (including prophylaxis) of obesity.

According to a further aspect of the invention, there is provided a pharmaceutical composition comprising a compound of formula (I) in combination with a pharmaceutically acceptable carrier or excipient and a method of making such a composition comprising combining a compound of formula (I) with a pharmaceutically acceptable carrier or excipient.

According to a further aspect of the invention, there is provided a method of preparing a compound of formula (I).

Compounds of the invention may be prepared by conventional methods as illustrated in the Reaction Schemes. R_1 to R_7 and X_1 to X_4 are as previously defined.

Reaction Scheme 1

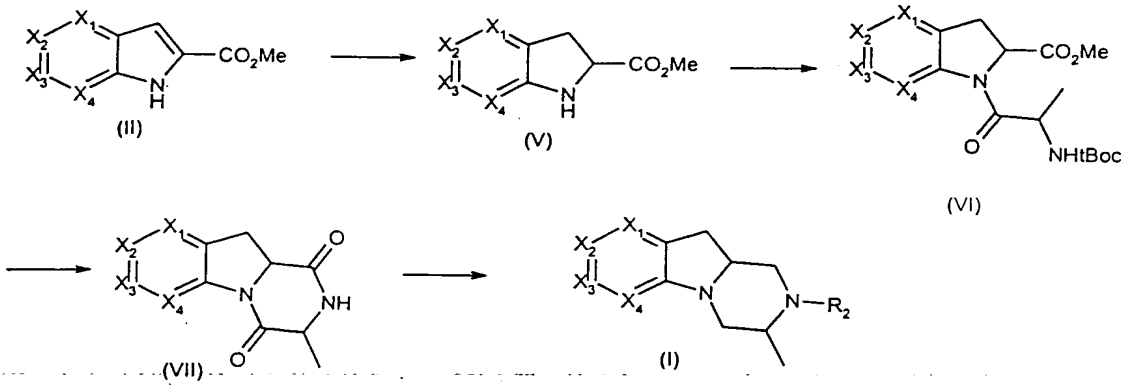


Compounds of formula (I), with X_1 to X_4 as previously defined and $R_1 = R_2 = R_3 = H$ are conveniently prepared as indicated in Reaction Scheme 1. The methyl 1-(cyanomethyl)-indole-2-carboxylate (III) can be obtained through reaction of the

sodium salt of indole carboxylate (II), prepared through treatment of (II) with a base such as sodium hydride in a solvent such as dimethylformamide with a cyanomethylation agent such as chloroacetonitrile. Reduction of (III) to the tetrahydropyrazino [1,2-a]indole (IV) may be achieved with a reducing agent such as lithium aluminium hydride in a suitable solvent such as ether. A compound of formula (I) can the be obtained by the subsequent reduction of the tetrahydropyrazino [1,2-a] indole (IV) with a reducing agent such as sodium cyanoborohydride in a suitable solvent such as acetic acid.

Compounds of formula (I), with X_1 to X_4 as previously defined and $R_1 = R_3 = H$ and R_2 = loweralkyl are conveniently prepared by standard methods such as reductive alkylation with an appropriate aldehyde or ketone in the presence of a reducing agent such as sodiumtriacetoxyborohydride, formic acid or sodium cyanoborohydride.

Reaction Scheme 2



Compounds of formula (I), with X_1 to X_4 as previously defined and $R_1 = R_2 = H$ and R_3 = Methyl are conveniently prepared as indicated in Reaction Scheme 2. The dihydroindole carboxylate (V) can be obtained from the indole carboxylate (II) through reduction with a reducing agent such as magnesium in methanol. The dihydro indole alanine ester derivative (VI) can be prepared by treatment of the dihydroindole (V) with a suitably protected alanine derivative such as tBoc-alanine in the presence of a

coupling agent such as dicyclohexylcarbodiimide (DCC) in a suitable solvent such as dichloromethane. The pyrazino[1,2-a]indole-1,4-dione derivative (VII) can subsequently be prepared by sequential treatment of (VI) with an acid such as hydrogen chloride in methanol followed by a base such as ammonia in methanol. Compounds of formula (I) can then be obtained by reduction of (VII) with a suitable reducing agent such as lithium aluminium hydride in a solvent such as tetrahydrofuran.

Compounds of formula (I), with X_1 to X_4 as previously defined and $R_1 = R_3 = H$ and R_2 = lower alkyl are conveniently prepared by standard methods such as reductive alkylation with an appropriate aldehyde or ketone in the present of a reducing agent such as sodiumtriacetoxyborohydride, formic acid or sodium cyanoborohydride.

If, in any of the other processes mentioned herein, the substituent group R_4, R_5, R_6 or R_7 is other than the one required, the substituent group may be converted to the desired substituent by known methods. The substituents R_4, R_5, R_6 or R_7 may also need protecting against the conditions under which the reaction is carried out. In such a case, the protecting group may be removed after the reaction has been completed.

The processes described above may be carried out to give a compound of the invention in the form of a free base or as an acid addition salt. If the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product of the process is a free base, an acid addition salt, particularly a pharmaceutically acceptable acid addition salt, may be obtained by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from basic compounds. Examples of acid addition salts are those formed from inorganic and organic acids, such as sulfuric, hydrochloric, hydrobromic, phosphoric, tartaric, fumaric, maleic, citric, acetic, formic, methanesulfonic, p-toluenesulfonic, oxalic, hippuric or succinic acids.

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, intranasal, parenteral

(*e.g.*, intravenous, intramuscular or subcutaneous) transdermal or rectal administratio: or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.* pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropylmethylcellulose); fillers (*e.g.* lactose, microcrystalline cellulose or calcium phosphate); lubricants (*e.g.* magnesium stearate, talc or silica); disintegrants (*e.g.* potato starch or sodium starch glycollate); or wetting agents (*e.g.* sodium lauryl sulfate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.* sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (*e.g.* lecithin or acacia); non-aqueous vehicles (*e.g.* almond oil, oily esters or ethyl alcohol); and preservatives (*e.g.* methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents.

Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, *e.g.* sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, *e.g.* dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A suitable dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (*e.g.*, obesity) is 0.1 to 500 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

The invention will now be described in detail with reference to the following examples. It will be appreciated that the invention is described by way of example only and modification of detail may be made without departing from the scope of the invention.

EXPERIMENTAL

Assay Procedures

1. Binding to serotonin receptors

The binding of compounds of formula (I) to serotonin receptors was determine *in vitro* by standard methods. The preparations were investigated in accordance with the assays given hereinafter.

Method (a): For the binding to the 5-HT_{2c} receptor the 5-HT_{2c} receptors were radiolabelled with [^{3}H]-5-HT. The affinity of the compounds for 5-HT_{2c} receptors in a CHO cell line was determined according to the procedure of D. Hoyer, G. Engel and H.O. Kalkman, *European J. Pharmacol.*, 1985, 118, 13-23.

Method (b): For the binding to the 5-HT_{2B} receptor the 5-HT_{2B} receptors were radiolabelled with [^{3}H]-5-HT. The affinity of the compounds for human 5-HT_{2B} receptors in a CHO cell line was determined according to the procedure of K. Schmuck, C. Ullmer, P. Engels and H. Lubbert, *FEBS Lett.*, 1994, 342, 85-90.

Method (c): For the binding to the 5-HT_{2A} receptor the 5-HT_{2A} receptors were radiolabelled with [^{125}I]-DOI. The affinity of the compounds for 5-HT_{2A} receptors in a CHO cell line was determined according to the procedure of D. J. McKenna and S. J. Peroutka, *J. Neurosci.*, 1989, 9/10, 3482-90.

The thus determined activity of the compound of the Example is shown in Table 1.

Table 1

Compound	**Method (a)** K_i **(2C)**	**Method (b)** K_i **(2B)**	**Method (c)** K_i **(2A)**
Example	31	32	53

2. Functional activity

The functional activity of compounds of formula (I) was assayed using a Fluorimetric Imaging Plate reader (FLIPR):

CHO cells expressing either the h5-HT_{2C}, h5-HT_{2A} or h5-HT_{2B} receptors were counted and plated into standard 96 well microtitre plates before the day of testing to give a confluent monolayer. The following day the cells were dye loaded with the calcium sensitive dye Fluo 3-AM by incubation with serum free culture maintenance media containing pluronic acid and Fluo 3-AM dissolved in DMSO at 37 °C in a CO_2

incubator at 95% humidity for approximately 90 minutes. Unincorporated dye was removed by washing with Hanks balanced salt solution containing 20mM HEPES and 2.5mM probenecid (the assay buffer) using an automated cell washer to leave a total volume of 100µl/well.

The drug (dissolved in 50µl of assay buffer) was added at a rate of 70µl/sec to each well of the FLIPR 96 well plate during fluorescence measurements. The measurements are taken at 1 sec intervals and the maximum fluorescent signal was measured (approx 10-15 secs after drug addition) and compared with the response produced by 10µM 5 -HT (defined as 100%) to which it is expressed as a percentage response (relative efficacy).Dose response curves were constructed using Graphpad Prism (Graph Software Inc.).

The thus determined activity of the Example is shown in Table 2.

Table 2

Compound	**h5-HT_{2C}**		**h5-HT_{2A}**		**h5-HT_{2B}**	
	EC_{50} (nM)	Relative Efficacy (%)	EC_{50} (nM)	Relative Efficacy (%)	EC_{50} (nM)	Relative Efficacy (%)
Example	18	91	513	53	39	61

3. Efficacy

The efficacy of 5-HT_{2C} agonists was assessed for ability to induce a specific syndrome.

The 5-HT_{2c} syndrome is a rapid screening method to assess the *in vivo* efficacy of 5-HT_{2c} agonists through their ability to induce three specific behaviours in rats. The animals are dosed with either a positive control (mCPP), test compound or vehicle, either s.c. or p.o.. The animals are observed on an open bench, typically 30, 60 and 180 minutes and the degree of syndrome is assessed over a two minute period on a scale of 0-3 depending on the presence and severity of splayed limbs, hunched posture and retro-pulsion, the three specific behaviours which constitute the syndrome. Data is analysed using Kruskal-Wallis Analysis of Variance followed with appropriate post-hoc

tests. All statistical analysis are conducted using Excel version 7.0 (Microsoft Corp and Statistica version 5.0 (Stasoft, Inc.).

The thus determined activity of the Example indicated that after a dose of 1mg/kg s.c. the compound maintains a significant pharmacological efficacy for at least 180 minutes.

4. Regulation of feeding behaviour

The *in vivo* activity of compounds of formula (1) was assayed for ability to regulate feeding behaviour by assaying food consumption in food deprived animals as follows.

Test compounds are assessed following acute administration. Each study utilises a between-subjects design (typically n=8) and compares the effects of doses of the test agent to those of vehicle and a positive control.

The anorectic drug d-fenfluramine normally serves as a positive control. The route of drug administration, drug volume and injection-test-interval are dependent upon the compounds used. A palatable wet mash, made by adding powdered lab chow and water in a ratio of 1:2 and mixing to a smooth consistency, is presented in 120 mL glass jars for 60 minutes each day. Intake is measured by weighing before and after each session. Care is taken to collect all spillage. Animals are allowed to habituate to the wet mash meal for 10 days. After drug administration, animals are allowed to consume the wet mash. Food consumption is assayed at pre-determined time points (typically 1, 2 and 4 hours after administration). Food intake data are subjected to one-way analysis of variance (ANOVA) with drug as a between-subjects factor. A significant main effect is followed up by the performance of Dunnett's test in order to assess which treatment mean(s) are significantly different from the control mean. All statistical analyses were performed using Statistica Software, Version 5.0 (Statsoft Inc.) and Microsoft Excel 7.0 (Microsoft Corp.).

The thus determined activity of the Example indicated that the compounds maintain significant hypophagia 3 hours after a dose of 1 mg/kg s.c.

Synthetic Examples

Example

8-Chloro-1,2,3,4,4a,5-hexahydropyrazino[*1,2-a*]indole hydrochloride

Methyl 6-chloro-1-(cyanomethyl)-indole-2-carboxylate

To a stirred solution of methyl 6-chloroindole-2-carboxylate (9.8 g, 46.7 mmol) (D. Knittel, *Synthesis*, 1985, 2, 186-188) in DMF (80 mL) under Ar at ambient temperature was added NaH (60% dispersion in mineral oil; 2.80 g, 70 mmol) portion-wise over 10 min. After 30 min, chloroacetonitrile (5.9 mL, 93.2 minol) was added dropwise and the resultant mixture was heated at 75 °C (bath temp.) for 45 min, then allowed to cool. The reaction mixture was poured onto ice (500 mL) and the solid product was filtered, washed with ice-cold water (100 mL), and triturated with refluxing EtOH (150 mL). After allowing to cool to ambient temperature, then cooling in ice, the solid product was filtered and washed with ice-cold EtOH (50 mL) to afford the *title compound* (9.49 g, 82 %) as a light grey solid: mp 177-8°C; IR ν_{max} (Nujol)/cm^{-1}; 3094, 2955, 2925, 2854, 1713, 1613, 1568, 1527, 1519, 1448, 1421, 1398, 1378, 1336, 1306, 1260, 1150, 1108, 1060, 943, 908, 834, 802, 761, 737, 682, 618, 597, 518, 478. NMR δ_H (400 MHz, DMSO-d_6) 3.95 (3H, s), 5.56 (2H, s), 7.22 (1H, dd, *J* 8.5, 2 Hz), 7.34 (1H, d, *J* 1 Hz), 7.43 (1H, br s) and 7.62 (1H, d, *J* 8.5 Hz).

*8-Chloro-1,2,3,4-tetrahydropyrazino[*1,2-a*]indole*

To a stirred suspension of $LiAlH_4$ powder (95 %; 1.18 g, 29.5 mmol) in anhydrous Et_2O (150 mL) under Ar at 14 °C was added portion-wise, over 20 min, methyl 6-chloro-1-(cyanomethyl)-indole-2-carboxylate (2.95 g, 11.86 mmol), allowing the internal temperature to stay at, or below 25 °C. After addition was complete, the mixture was heated at reflux for 18 h, then allowed to cool. Water (1.18 mL) was cautiously added, followed by 15 % aqueous NaOH (1.18 mL), then water (3.5 mL). After stirring for 30 min, $MgSO_4$ was added and the mixture was filtered through Kieselguhr and washed through with Et_2O (50 mL). The solvent was removed *in vacuo* and the residue was purified by flash chromatography [SiO_2; 9(EtOAc) : 1(MeOH)] to afford the *title compound* (1.38 g, 56%) as a pale yellow solid: NMR δ_H (400 MHz, $CDCl_3$) 1.64 (1H,

br s), 3.35 (2H, t, *J* 5.5 Hz), 3.96 (2H, t, *J* 5.5 Hz), 4.19 (2H, d, *J* 1.0 Hz), 6.16 (1H, d, 1.0 Hz). 7.04-7.08 (1H, m), 7.23-7.26 (1H, m), and 7.43 (1H, d, *J* 8.5 Hz).

*8-Chloro-1,2,3,4-tetrahydropyrazino[*1,2-a*]indole fumarate*

To a solution of 8-chloro-1,2,3,4-tetrahydropyrazino[*1,2-a*]indole (130 mg, 0.63 mmol) in 2-propanol (4 mL) was added fumaric acid (110 mg, 0.95 mmol) and the mixture was heated to reflux for 1 min. The resultant suspension was allowed to cool to ambient temperature, and then cooled in ice. The solid was filtered and washed with ice-cold 2-propanol (3 mL) to afford the *title compound* (184 mg, 90%) as a pale yellow solid: mp 202.5 °C (decomp.); NMR δ_H (400 MHz, DMSO-d_6) 3.26 (2H, t, *J* 5.5 Hz), 4.01 (2H, t, *J* 5.5), 4.12 (2H, s), 7.01 (1H, dd, *J* 8.0, 2.0 Hz) and 7.45-7.49 (2H, m); Anal. Calcd for $C_{15}H_{15}ClN_2O_4$: C, 55.82; H, 4.68; N, 8.68%. Found: C, 55.90; H, 4.72; N, 8.58%.

*8-Chloro-1,2,3,4,4a,5-hexahydropyrazino[*1,2-a*]indole*

To a stirred solution of 1,2,3,4-tetrahydropyrazino[*1,2-a*]indole (1.185 g, 5.73 mmol) in AcOH (40 mL) under Ar at 10 °C was added portion-wise over 5 min sodium cyanoborohydride (1.19 g, 18.94 mmol). The resultant mixture was allowed to warm to ambient temperature, and was stirred for 24 h. The mixture was poured into water (200 mL) and was basified (pH 8-9) by the careful addition, with cooling, of NH_4OH (60 mL) over 5 min. The basified mixture was extracted with $CHCl_3$ (3 × 200 mL), the combined organic extracts washed with brine (200 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography [SiO_2; 90(EtOAc) : 8(MeOH) : 2(NH_4OH)] to afford the *title compound* (768 mg, 64 %) as a colourless oil: NMR δ_H (400 MHz, $CDCl_3$) 1.60 (1H, br s), 2.50 (1H, ddd, *J* 15.1, 9.0, 1.0 Hz), 2.74 (1H, dd, *J* 11.5, 10.5 Hz), 2.79-2.99 (4H, m), 3.04 (1H, dd, *J* 11.5, 3.5 Hz), 3.42-3.52 (2H, m), 6.37 (1H, d, *J* 2.0 Hz), 6.57 (1H, dd, *J* 7.5, 2.0 Hz) and 6.92-6.96 (1H, m).

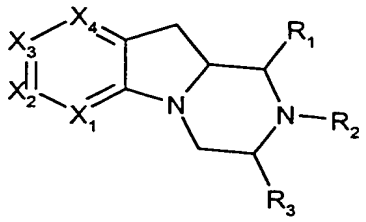
*8-Chloro-1,2,3,4,4a,5-hexahydropyrazino[*1,2-a*]indole hydrochloride*

To a solution of 8-chloro-1,2,3,4,4a,5-hexahydropyrazino[*1,2-a*]indole (747 mg, 3.58 mmol) in acetone (4 mL) was added an ethereal solution of HCl (1 M; 10.75 mL, 10.75 mmol) followed by Et_2O (4 mL). The resultant solid was filtered and washed with ice-cold Et_2O (10 mL) to afford the *product* (850 mg, 97 %) as a white solid: mp 235 °C

(decomp.); NMR δ_H (400 MHz, DMSO-d_6) 2.59 (1H, dd, *J* 15.5, 7.0 Hz), 2.83 (1H, t, *J* 12 Hz), 2.86-2.95 (1H, m), 3.01 (1H, dd, *J* 15.5, 8.0 Hz), 3.15-3.36 (4H, m), 3.80-3.90 (2H, m), 6.65 (1H, dd, *J* 7.5, 2 Hz), 6.70 (1H, d, *J* 2 Hz), 7.08 (1H, d, *J* 7.5 Hz) and 9.45 (2H, br s); Anal. Calcd for $C_{11}H_{14}Cl_2N_2$: C, 53.89; H, 5.76; N, 11.42%. Found: C, 53.88; H, 5.90; N, 11.26%.

CLAIMS

1. A chemical compound of formula (I):



(I)

wherein:

R_1 to R_3 are independently selected from hydrogen and lower alkyl;

X_1 is selected from N and C-R_4;

X_2 is selected from N and C-R_5;

X_3 is selected from N and C-R_6;

X_4 is selected from N and C-R_7;

R_4, R_5 and R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, alkoxy, aryloxy, alkoyl, aryloyl, alkylthio, arylthio, alkylsulfoxyl, arylsulfoxyl, alkylsulfonyl, arylsulfonyl, amino, alkylamino, dialkylamino, nitro, cyano, carboalkoxy, carboaryloxy and carboxy;

R_6 is selected from hydrogen, halogen, alkyl, aryl, aryloxy, alkylthio, arylthio, alkylsulfoxyl, arylsulfoxyl, alkylsulfonyl, arylsulfonyl, amino, alkylamino, dialkylamino and cyano; with the proviso that R_4 to R_7 are not all selected as hydrogen.

2. A compound according to claim 1 wherein R_1, R_2 and R_3 are independently selected from hydrogen and methyl.

3. A compound according to claim 2 wherein R_2 is hydrogen.

4. A compound according to claim 3 wherein R_1, R_2 and R_3 are hydrogen.

5. A compound according to any preceding claim wherein X_2 is C-R_5.

6. A compound according to any preceding claim wherein X_3 is C-R_6.

7. A compound according to any preceding claim wherein X_4 is C-R_7.

8. A compound according to any preceding claim wherein X_1 is C-R_4.

9. A compound according to any preceding claim wherein two of R_4, R_5, R_6 and R_7 are hydrogen.

10. A compound according to any preceding claim wherein two of R_4, R_5, R_6 and R_7 are independently selected from hydrogen, chlorine, fluorine, trifluoromethyl and bromine.

11. A compound according to claim 10 wherein at least one of R_5 and R_6 is selected from chlorine, fluorine, trifluoromethyl and bromine.

12. A compound of formula (I) as set out in any one of claims 1 to 11 for use in therapy.

13. The use of a compound of formula (I) as set out in any of claims 1 to 11 in the manufacture of a medicament for the treatment of disorders of the central nervous system; damage to the central nervous system; cardiovascular disorders; gastrointestinal disorders; diabetes inspidus, and sleep apnea.

14. A use according to claim 13 wherein the disorders of the central nervous system are selected from depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioural disorders, behavioural disorders associated with dementia, organic mental disorders, mental disorders in childhood, aggressivity, age-related memory disorders,

chronic fatigue syndrome, drug and alcohol addiction, obesity, bulimia, anorex nervosa and premenstrual tension.

15. A use according to claim 13 wherein the damage to the central nervous system is by trauma, stroke, neurodegenerative diseases or toxic or infective CNS diseases.

16. A use according to claim 15 wherein said toxic or infective CNS disease is encephalitis or meningitis.

17. A use according to claim 13 wherein the cardiovascular disorder is thrombosis.

18. A use according to claim 13 wherein the gastrointestinal disorder is dysfunction of gastrointestinal motility

19. A use according to claim 13 wherein said medicament is for the treatment of obesity.

20. A use according to any one of claims 10 to 19 wherein said treatment is prophylactic treatment.

21. A method of treatment of any of the disorders set out in claims 13 to 18 comprising administering to a patient in need of such treatment an effective dose of a compound of formula (I) as set out in any one of claims 1 to 11.

22. A method of treatment according to claim 21 wherein said disorder is obesity.

23. A method according to claim 21 or 22 wherein said treatment is prophylactic treatment.

24. A method of preparing a compound of formula (I) as set out in any one of claims 1 to 11.

25. A pharmaceutical composition comprising a compound of formula (I) as set out in any one of claims 1 to 11 in combination with a pharmaceutically acceptable carrier or excipient.

26. A method of making a composition according to claim 22 comprising combining a compound of formula (I) as set out in any one of claims 1 to 11 with a pharmaceutically acceptable carrier or excipient.

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31-1-00

Compmath v Rowland